Clinical Trial Enrollment: NIH Experience

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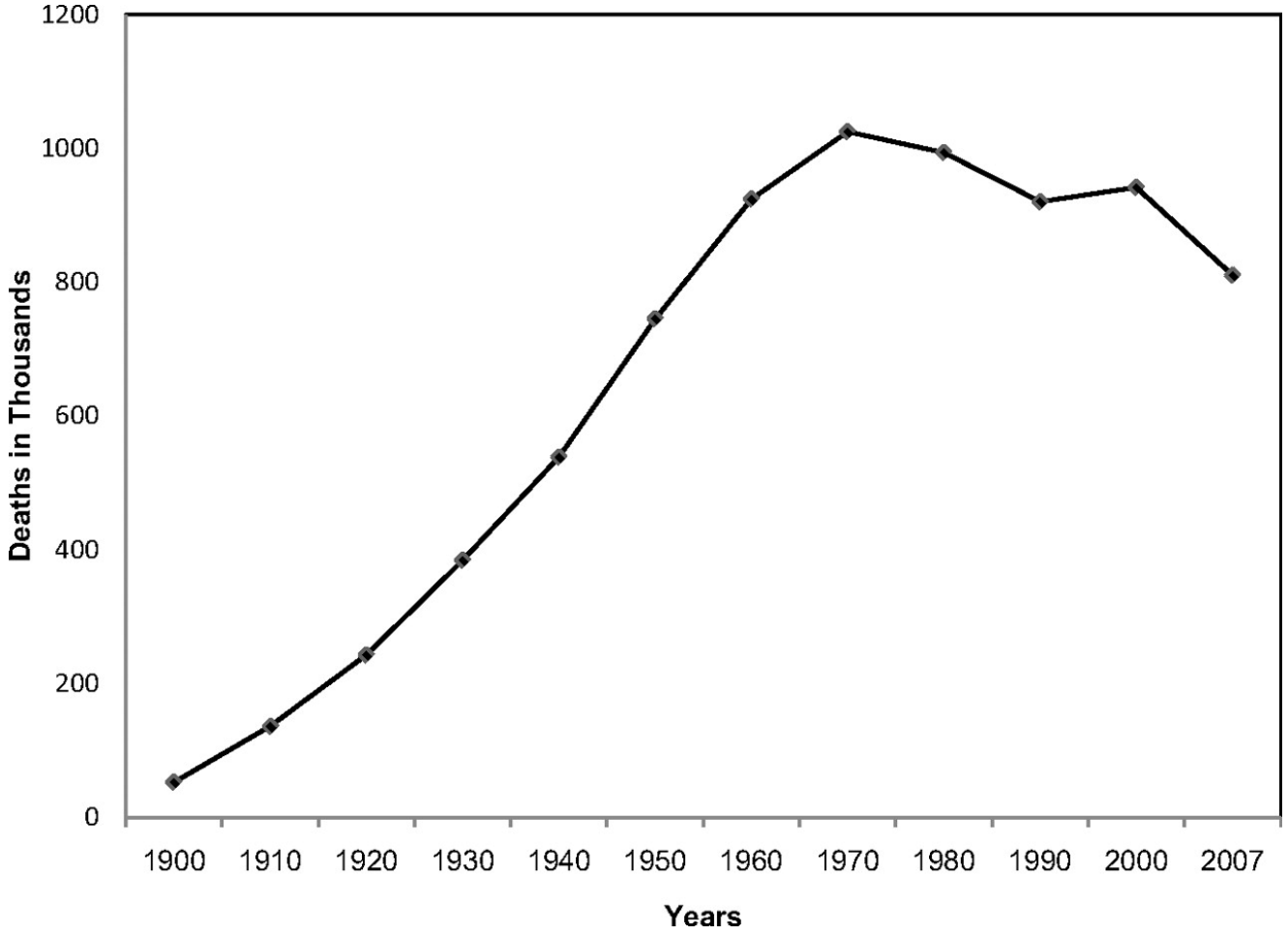
Objectives: Clinical Trial Enrollment

- Understanding why inclusion is important
  - Cardiovascular Disease Burden
  - Sex and Racial Disparities in CV
  - Presentation of Cardiovascular Disease
  - Treatment of Cardiovascular Disease
  - Cardiovascular Disease Outcomes
- Challenges to clinical research
  - Historical perspective and current attitudes
  - Awareness and behavior of general public and providers
  - Communication and cooperation of stakeholders
- Overcoming Challenges

Life Expectancy by Race and Sex, US 2008

Age (Years)	Total	Male	Female	Total White	White Male	White Female	Total Black	Black Male	Black Female
Birth	78.0	75.5	80.5	78.4	75.9	80.8	74.3	70.9	77.4
15	63.8	61.3	66.1	64.0	61.6	66.3	60.6	57.2	63.6
35	44.7	42.6	46.7	44.9	42.8	46.9	41.8	39.0	44.3
65	18.7	17.2	19.9	18.7	17.3	19.9	17.5	15.5	18.9
75	11.7	10.6	12.5	11.6	10.6	12.4	11.3	10.0	12.2

Deaths from CVD: US, 1900-2007



Roger V L et al. *Circulation.* 2011;123:e18-e209

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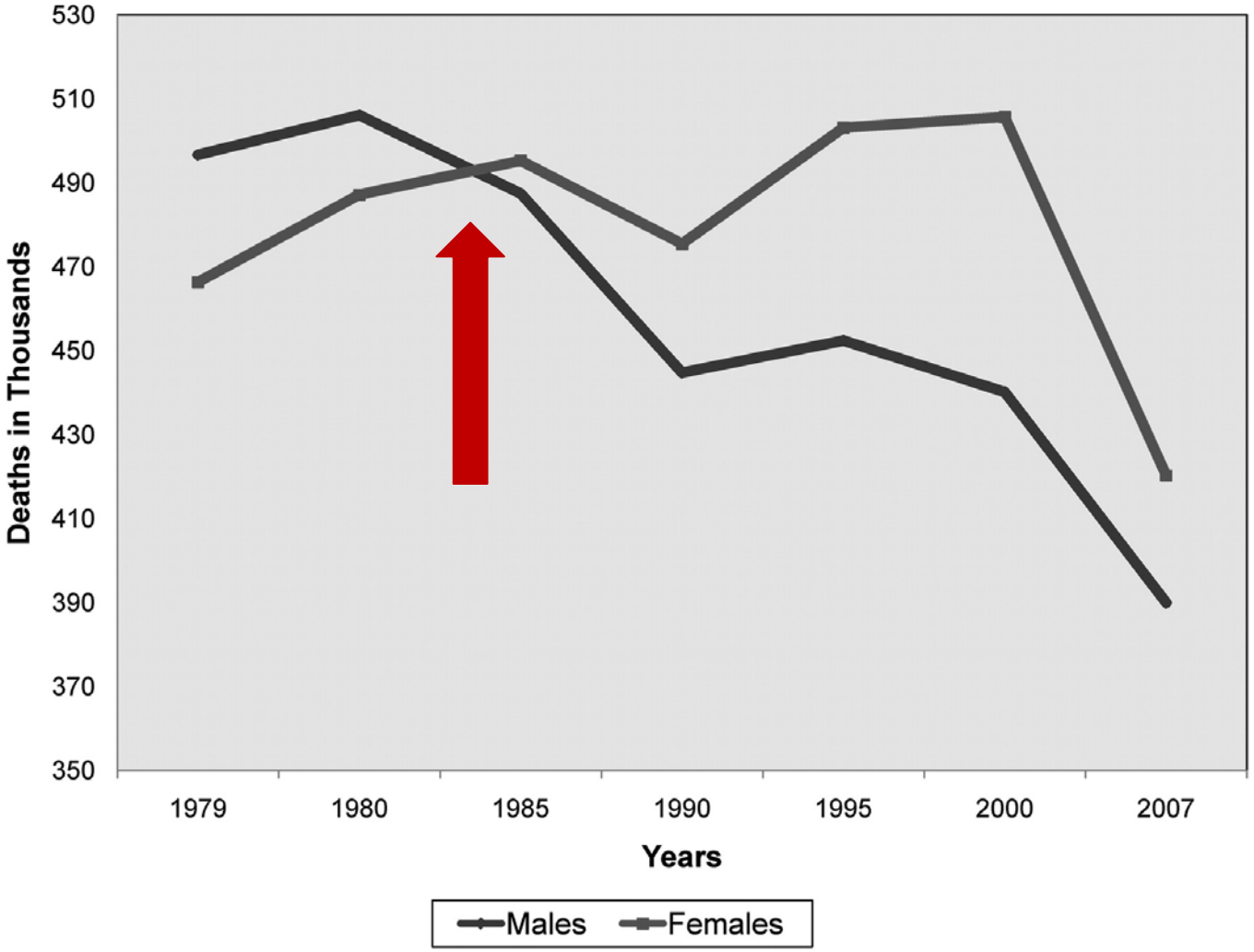
Sex Differences in Cardiovascular Mortality US 1979–2007



Roger V L et al. *Circulation.* 2011;123:e18-e209

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Risk Factors for Women

- Under-perception of risk
- Older age at presentation
- Framingham risk score may underestimate risk
- Emerging risk factors - pregnancy complications and rheumatologic disease
- Higher risk factor and co-morbidity burden
- 25% increased coronary artery disease risk among female smokers as compared to male smokers
- Disproportionate increased coronary artery disease risk for diabetic women versus diabetic men

1. Mosca et al. *Circulation*. 2011;123:1243-1262.
2. Huxley et al. *Lancet.* 2011;378:1297–1305.
3. NHLBI Chartbook 2012.
4. Huxley et al. *BMJ*. 2006;332:73-78.

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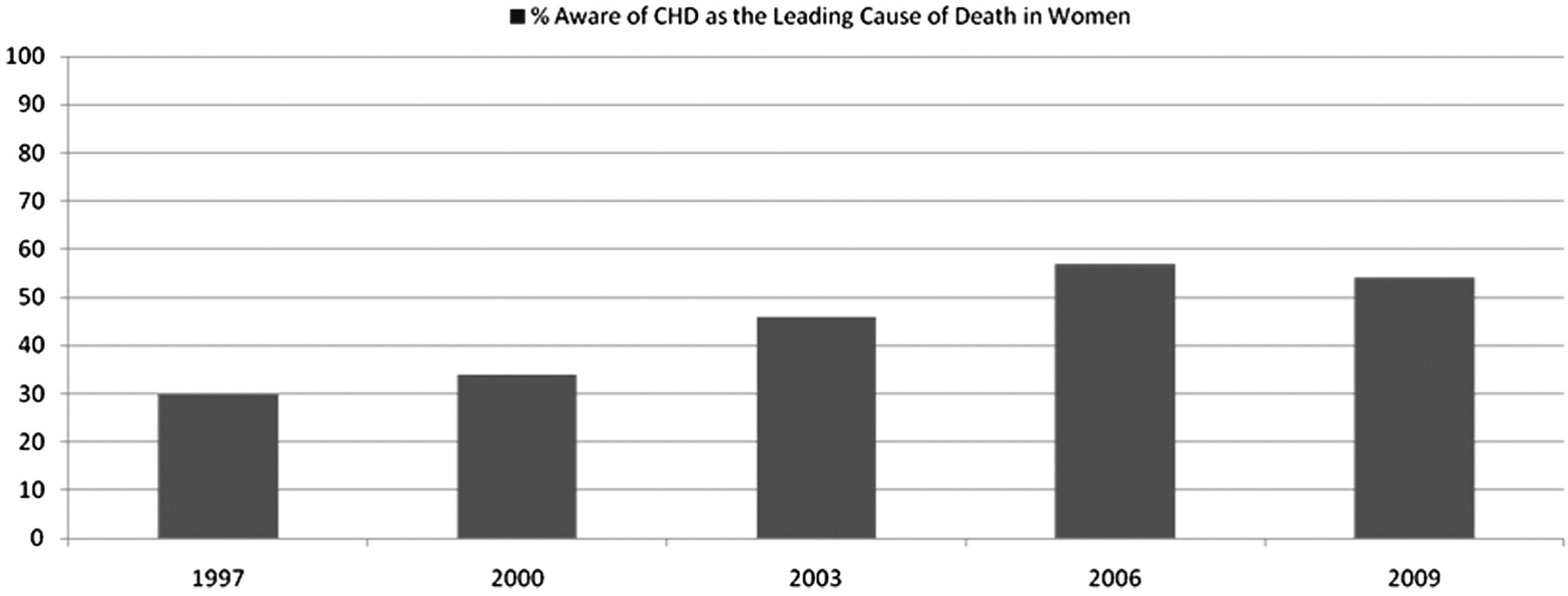
Under-Perception of Risk

Trends in awareness that coronary heart disease is the leading cause of death in women



Mosca L et al. *Circ Cardiovasc Qual Outcomes.* 2010;3:120-127

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Sex/Gender Differences in the Burden of CVD

Adapted from Mosca L et al. *Circulation.* 2011;124:2145-2154

	Men	Women
Remaining lifetime risk for CVD at age 40 y	2 in 3	1 in 2
CVD		
Deaths - CVD and congenital heart disease (2007)	391,886	421,918
Age-adjusted CVD death rate per 100,000 (2007)	300.3	211.6
Prevalence of CVD (2008, age ≥20 y), in millions	39.9 (37.4%)	42.7 (35.0%)
Hospital discharges for CVD (2007)	3,016,000	2,874,000
Coronary Heart Disease		
Deaths caused by CHD (2007)	216,050	190,301
Age-adjusted CHD death rate per 100,000 (2007)	165.4	95.7
Prevalence of CHD (2008, age ≥20 y), in millions	8.8(8.3%)	7.5 (6.1%)
Hospital discharges for CHD (2007)	965,000	607,000
Stroke		
Deaths resulting from stroke (2007, all ages)	54,111	81,841
Age-adjusted stroke death rate per 100,000	42.5	41.3
Prevalence of stroke (2008, age ≥20 y), in millions	2.8 (2.7%)	4.2 (3.3%)
Hospital discharges for stroke (2007)	371,000	458,000
Heart failure		
Prevalence of heart failure (2008, age ≥20 y), in millions	3.1 (3.0%)	2.6 (2.0%)
Hospital discharges for heart failure (2007, all ages)	470,000	520,000

Clinical Presentation

- Under-recognition of symptoms
- Differing mechanisms of disease
- Angina
  - Major presentation of coronary disease among women as compared to myocardial infarction among men
  - 20% higher rate as compared to men and higher rate of MI
  - 2x morbidity and mortality
- Acute Coronary Syndrome
  - Subtypes differ: Fewer women then men present with STEMI, but more with Unstable Angina
  - When present with MI, more likely than men to not have chest pain
  - Older, more co-morbidities, and more severe clinical status on presentation
  - Less severe obstructive disease at angiography
- Sudden Cardiac Death
  - More likely to die of cardiac arrest before hospital arrival (52% vs. 43%)

1. Wenger et al. *Circulation*. 2012;126:604-611.
2. Jneid H et al. *Circulation.* 2008;118:2803-2810.
3. Gulati M. et al. *Arch Intern Med*. 2009;169(9):843-850.
4. Mega J et al. *Circulation*. 2010;121:1809-1817.
5. Hemingway H et al. *Circulation.* 2008;117:1526-1536

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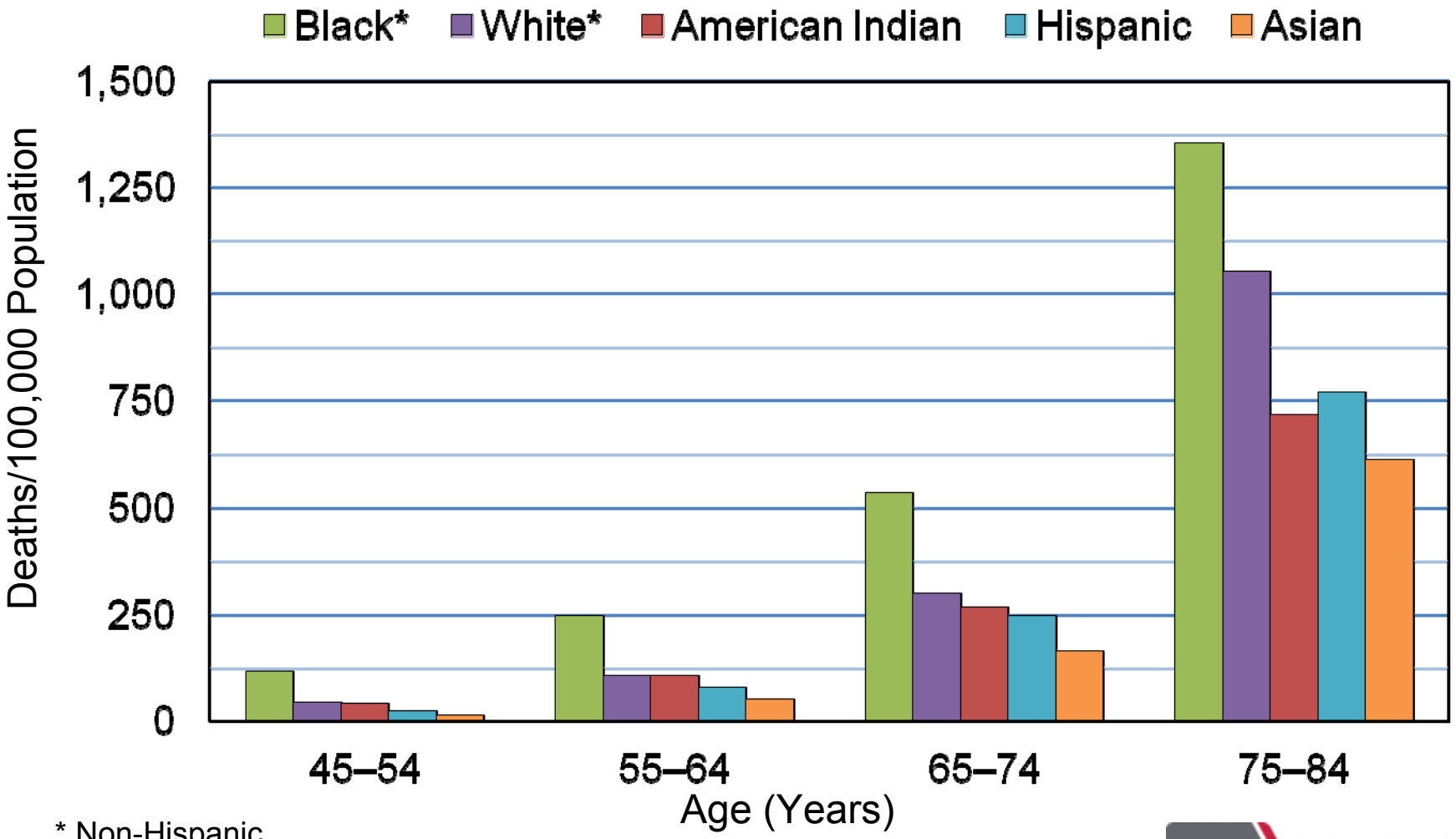
Death Rates for Heart Disease in Females by Age & Race/Ethnicity, U.S., 2008



* Non-Hispanic

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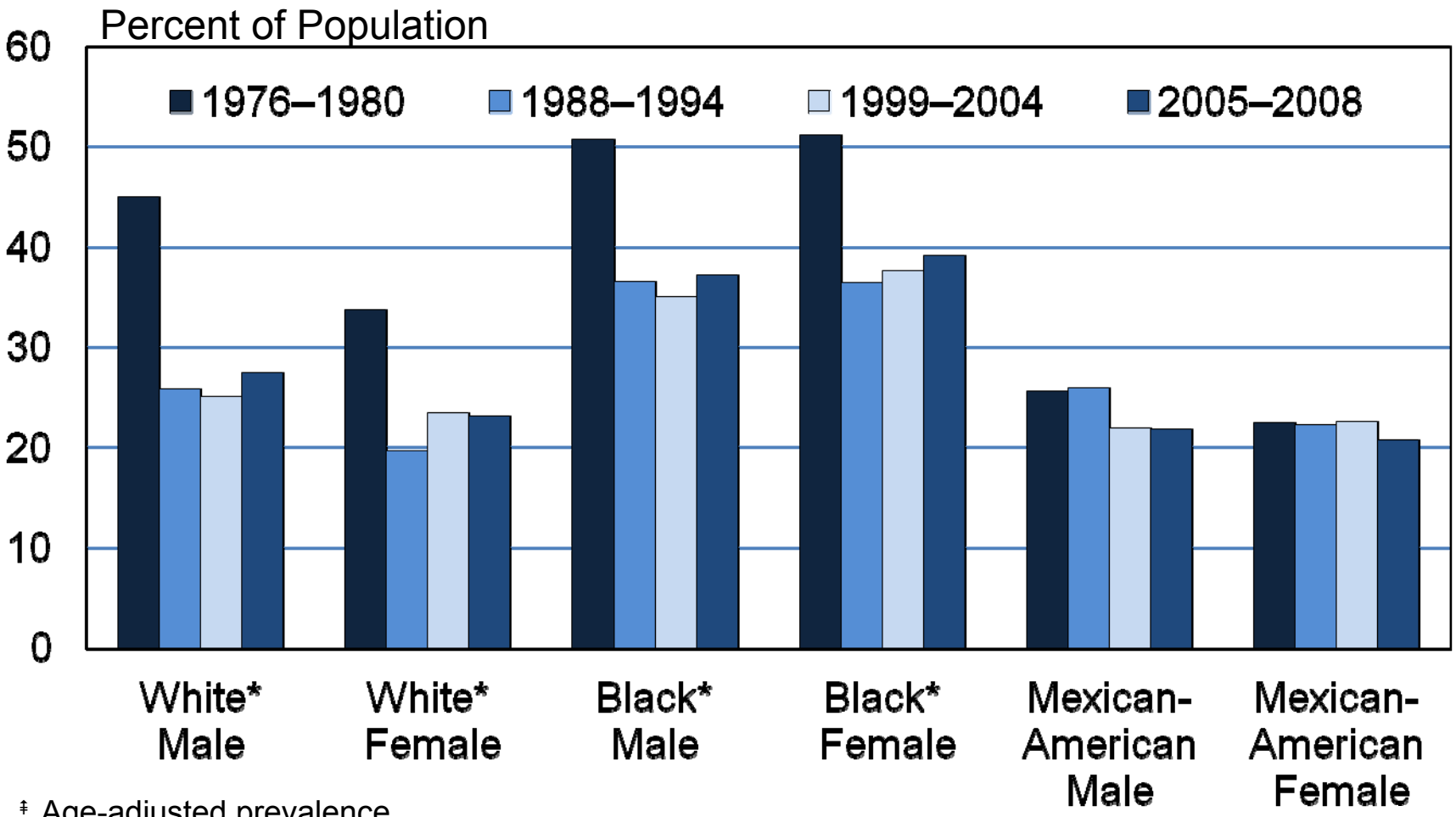
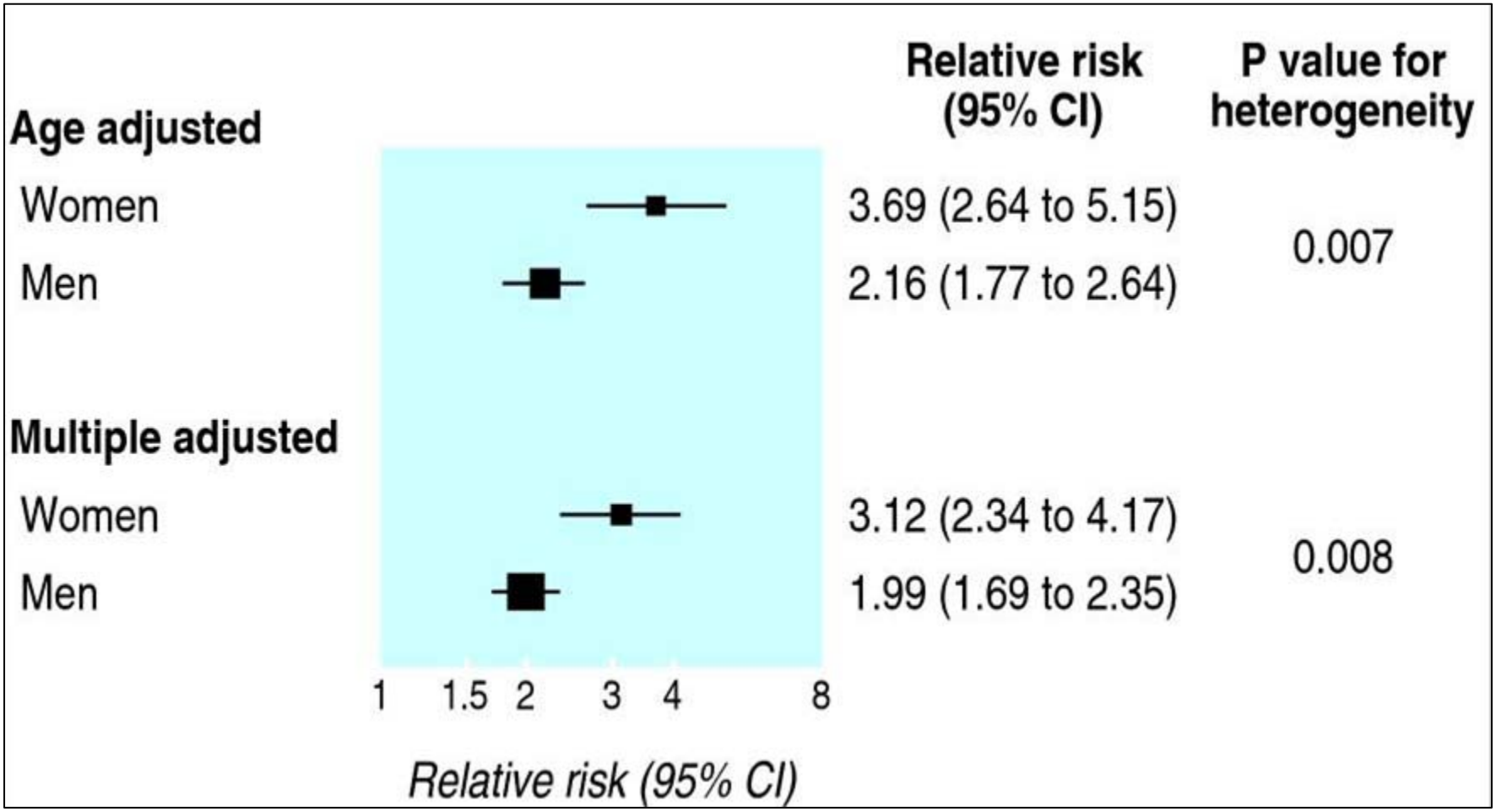
Hypertension‡ by Race/Ethnicity & Sex, Ages 20–74, U.S., 1976–1980 to 2005–2008



‡ Age-adjusted prevalence.
Hypertension: systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or on medication.
* Non-Hispanic.

Fatal Coronary Heart Disease in Men and Women With Diabetes



Huxley R. *BMJ*. 2006;332:73-78.

Treatment

- Stable Ischemic Disease
  - Lower rates of standard therapies
  - Higher rates of repeat angiography
- Acute Coronary Syndrome
  - Underutilization of guideline-based therapy
    - Absence of obstructive disease may account for therapeutic underutilization (equivalent drug use once obstruction diagnosed)
  - Less angiography and revascularization in this setting
  - Under-enrollment in clinical trials
    - Lack of evidence raises questions in women (e.g., survival benefit for early invasive strategy in women with USA/NSTEMI)

1. Wenger et al. *Circulation*. 2012;126:604-611.
2. Jneid H et al. *Circulation*. 2008;118:2803-2810.
3. Dhruva et al. *Circ Cardiovasc Qual Outcomes.* 2011;4:165-171.

Clinical Performance Measures, Invasive Procedures, and In-Hospital Death

Measure/Treatment/Outcome	N	Adjusted OR (95% CI) (Women vs. Men)	P
Early medical therapy			
Aspirin within 24 h	70 360	0.86 (0.81–0.90)	<0.0001
β-Blocker within 24 h	64 681	0.90 (0.86–0.93)	<0.0001
Invasive procedures			
Cardiac catheterization	74 769	0.91 (0.88–0.94)	<0.0001
PCI	67 477	0.78 (0.74–0.81)	<0.0001
CABG	67 477	0.60 (0.55–0.65)	<0.0001
Revascularization	67 477	0.68 (0.65–0.71)	<0.0001
Acute reperfusion and timeliness for STEMI			
DTN ≤30 min	2807	0.78 (0.65–0.92)	0.004
DTB ≤90 min	7673	0.87 (0.79–0.95)	0.004
Reperfusion therapy	24 742	0.75 (0.70–0.80)	<0.0001
Primary PCI	24 742	0.83 (0.78–0.87)	<0.0001
Fibrinolytic therapy	24 742	0.87 (0.81–0.93)	<0.0001
In-hospital death			
Overall AMI cohort	70 105	1.04 (0.99–1.10)	0.1
STEMI subpopulation	23 015	1.12 (1.02–1.23)	0.015

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Outcomes

- Angina
  - Higher standardized mortality due to CHD than men
  - Women with MI more likely than men to have a recurrent MI
- Acute Coronary Syndrome
  - Higher unadjusted mortality and complication rates post ACS
    - Once adjusted for age and co-morbidity, literature inconsistent
  - Specific subsets more affected
    - Women <50 yrs, 2x mortality after MI
    - STEMI as compared to NSTEMI
  - 2x mortality after CABG, particularly women <50 yrs
  - Higher PCI mortality rate yet comparable angiographic success
  - Excess bleeding complications
    - Lack of evidence raises questions (IIb/IIIa inhibitors when no PCI)
- Heart Failure
  - Women with MI more likely than men to have heart failure

1. Wenger et al. *Circulation*. 2012;126:604-611.
2. Jneid H et al. Circulation 2008;118:2803-2810.
3. Gulati M. et al. *Arch Intern Med*. 2009;169(9):843-850.
4. Mega J et al. *Circulation*. 2010;121:1809-1817.
5. Hemingway H et al. *Circulation* 2008;117:1526-1536
6. Canto et al. *JAMA* 2012;307:813-822.

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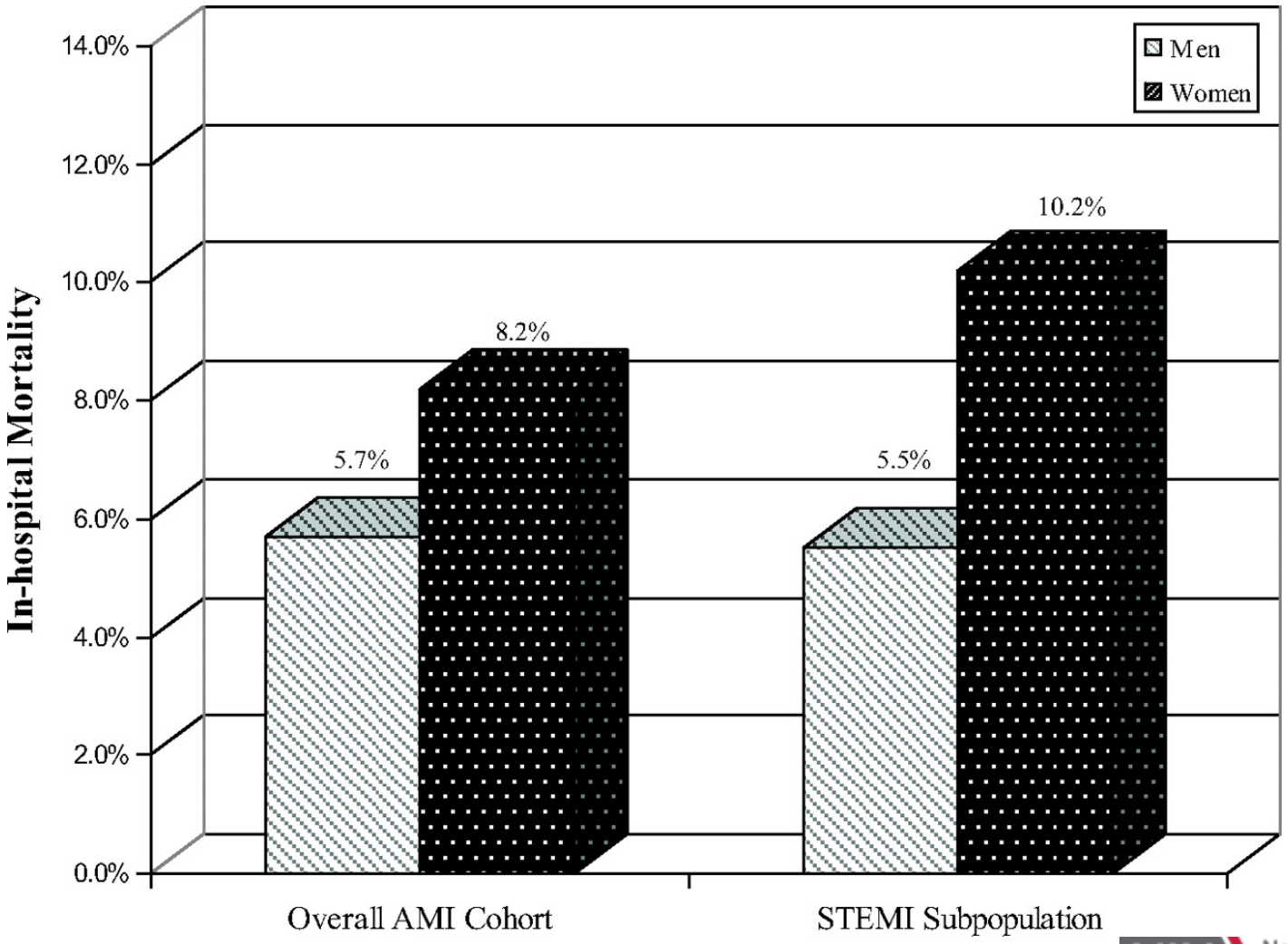
In-hospital Mortality Among Patients Hospitalized with Acute Myocardial Infarction



Jneid H et al. *Circulation.* 2008;118:2803-2810

Important Milestones

- 1992 NHLBI Conference on CV Health and Disease in Women
- 2003 AHRQ Report on Diagnosis and Treatment of CHD in Women
  - Systematic review of research that highlighted that much of the evidence supporting recommendations for women is extrapolated from studies conducted predominantly in middle-aged men
  - Emphasized need for enrollment of women in trials
- 2010 IOM Report on Women's Health Research
  - Documented that women are underrepresented in research studies
  - Found limitations in design, analysis, and reporting of scientific studies
  - Underscored importance of disproportionate burden of disease among disadvantaged women
  - Recommended inclusion of focus on quality of life in research on women
- Unintended consequences of inclusion/exclusion criteria

Sex Differences in Medical Device Trials

- Among 78 high-risk CV devices approved 2000-2007
  - Study populations: mean of 67% men
  - No increase in enrollment of women over time
  - 28% of device studies without reported sex distribution
- Sex specific analysis present in 41% of studies
  - When performed 26% identified difference in safety or effectiveness
- Consequences - Meta-analyses of RCTs
  - Lack of survival benefit for an early invasive strategy in women with USA/NSTEMI
  - Lack of efficacy of IIb/IIIa inhibitors in ACS with no planned PCI
  - Lack of survival benefit (all-cause mortality) for ICDs for primary prevention

Dhruva et al. *Circ Cardiovasc Qual Outcomes.* 2011;4:165-171

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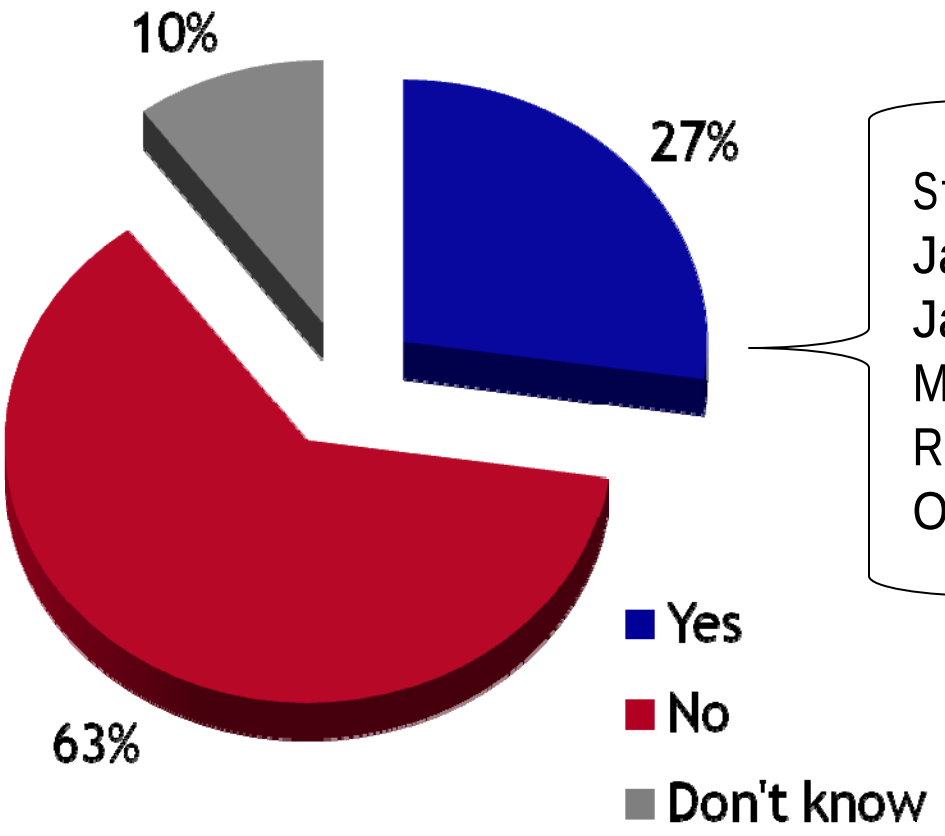
Landmark CV Research in Women

- NHLBI Women's Health Initiative
  - Menopausal hormone replacement therapy did not prevent incident or recurrent CVD in women and increased risk of CVA
- NHLBI Women's Ischemia Syndrome Evaluation Study
  - Identified MI with adverse clinical outcomes in women in the absence of obstructive disease in epicardial coronary arteries

Awareness and attitudes

Most Americans Can't Name a Living Scientist

Can you name any living scientists? (% total volunteered responses)



Stephen Hawking	13%
James Watson	2%
Jane Goodall	2%
Michio Kaku	1%
Richard Dawkins	1%
Other	14%

Respondents: 1,000

Source: National Poll, May 2010
Charlton Research Company for Research!America

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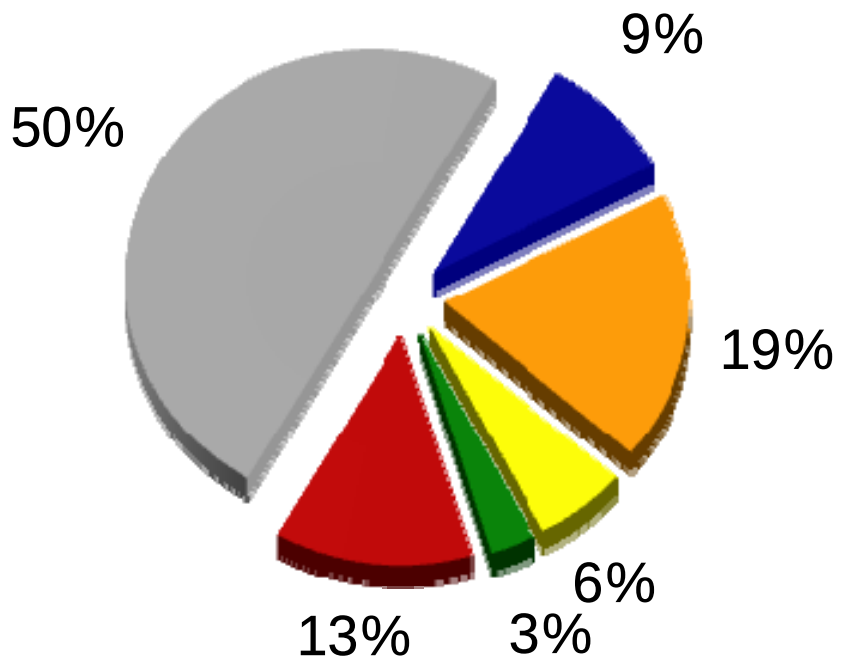
Few Americans Recognize the National Institutes of Health

What is the name of the government agency that funds most of the medical research paid for by taxpayers in this country? (first volunteered responses)



Source: Research Enterprise Poll, February 2010
CharIton Research Company for Research!America

Respondents: 1,000

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Public Perceptions of Science and Scientists

Science's impact on society is:

- Mostly positive 84%
- Mostly negative 6%
- Other/don't know 10%

Professions contributing "a lot to society's well-being":

- Members of military 84%
- Teachers 77%
- Scientists 70%
- Medical doctors 69%

Respondents: 2,001

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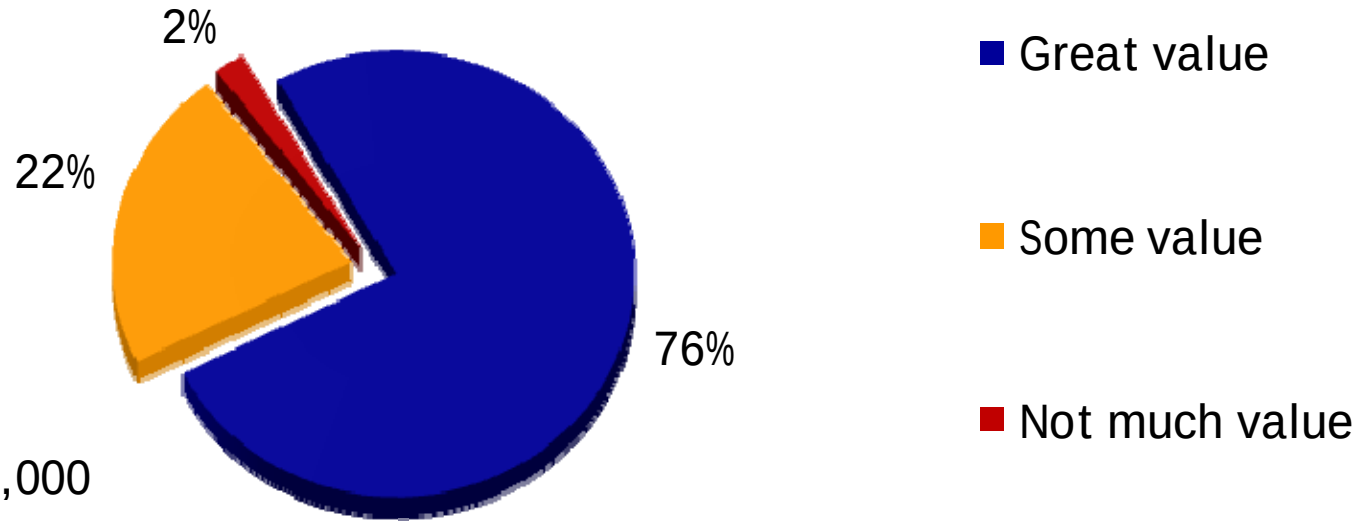
Pew Research Center for the People & the Press, July 2009

Clinical Research is a Great Value

One kind of research, often referred to as clinical trials, is clinical research. In this, patients choose to participate to test the safety and effectiveness of certain treatments, drugs or devices. How important is this kind of research? Would you say it is of…



Respondents: 1,000

Source: Research Enterprise Poll, February 2010
Charlton Research Company for Research!America

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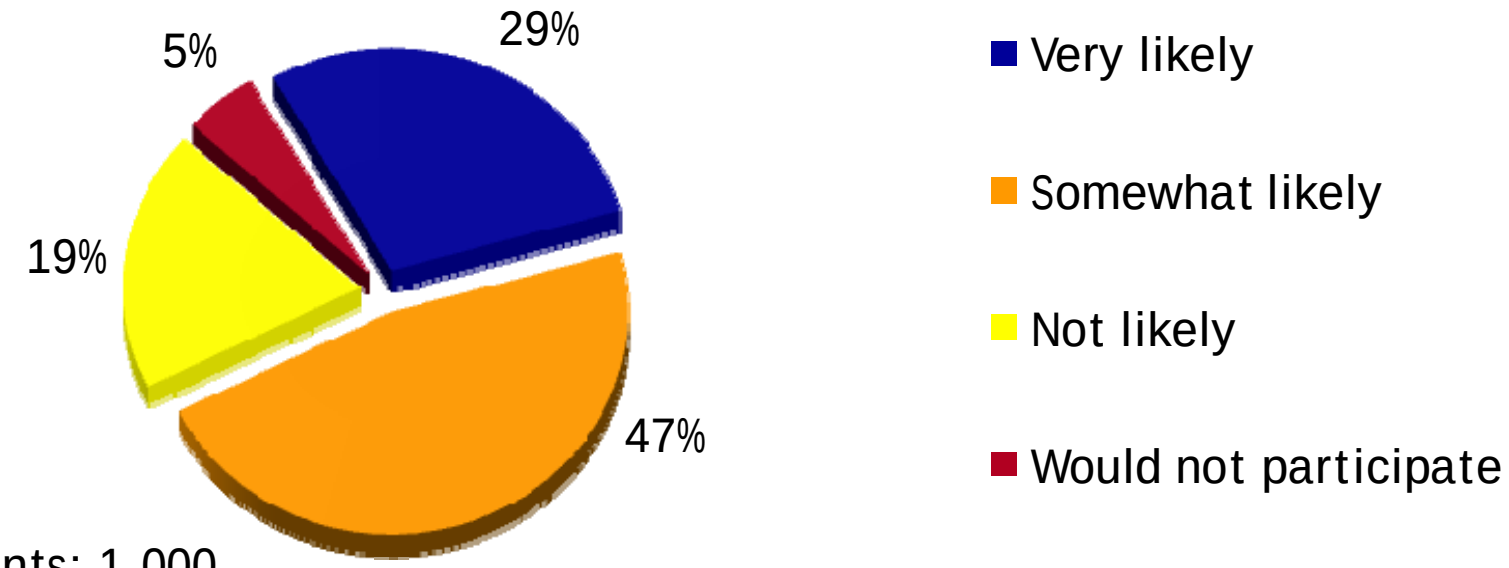
Many Americans Likely to Volunteer for Clinical Research

Please consider your own possible participation as a volunteer in clinical research. How likely would you be to participate in a clinical research study?



Respondents: 1,000

Source: Research Enterprise Poll, February 2010
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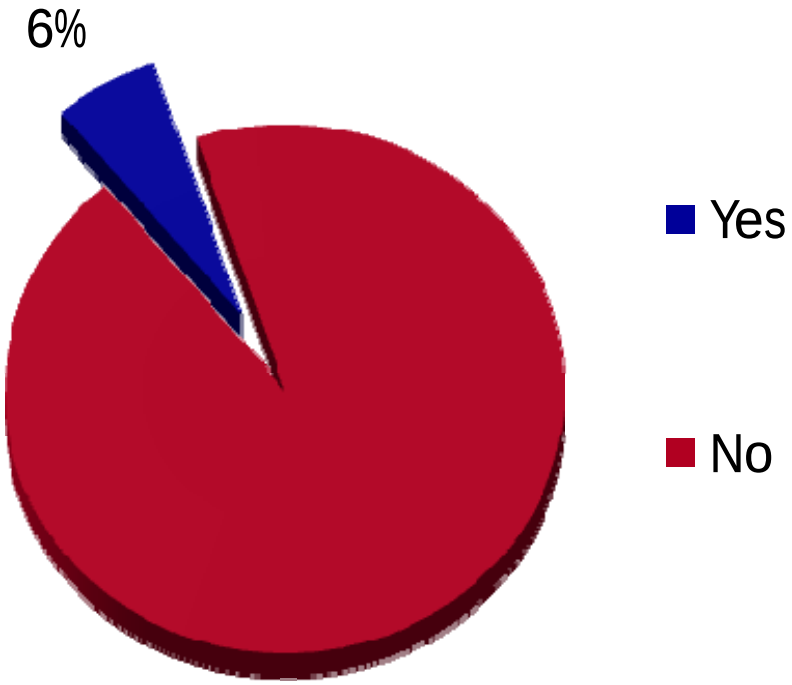
Most Doctors Do Not Suggest Participating in Clinical Research

Has your doctor ever suggested that you participate in a clinical research study?



Respondents: 1,000

Source: Research Enterprise Poll, February 2010
CharIton Research Company for Research!America

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Public Perceptions of Clinical Trials (Slide 1)

"Using the scale below, please indicate how strongly you agree or disagree with the statements below. People who participate in clinical research studies…"

Percent saying strongly or somewhat agree:

Are making a contribution to science	86%
Are part of an experiment to test medications/treatments not already available to the public	79%
Learn more about their condition and health in general	76%
Have a chance to get free medicine	65%
Do not have to pay for medical care	53%

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Source: Harris Interactive Healthcare Research. 2005; 5, Issue 6: 9.

Clinical Trials: More Perceptions (Slide 2)

- 76% said they expected their treating physician to inform them about current trials
- 91% said they wanted to be informed about the results of the study; if they were not informed, 68% would refuse to participate.

Respondents: 400

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Source: Mayo Clinic Proceedings. 2009: 84, no. 3: 243-247.

Clinical Trials: More Perceptions (Slide 1)

- 93% said they believed that all possible measures would be taken to protect their safety; 94% said they believed that all possible measures would be taken to protect their privacy.
- 56% said that clinical trials sponsored by a pharmaceutical company would likely have a conflict of interest.

Respondents: 400

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Clinical Trials: Risks

Which of the following do you consider to be the greatest risk of participating in a clinical research study?

Possible side effects	47%
Health risks	32%
Unproven therapy	9%
Receiving a placebo (sugar pill)	5%
Privacy concerns	2%
Other	1%
None; I do not believe there are any risks	4%

Respondents: 2,261

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Source: Harris Interactive Healthcare Research. 2005; 5, Issue 6: 9.

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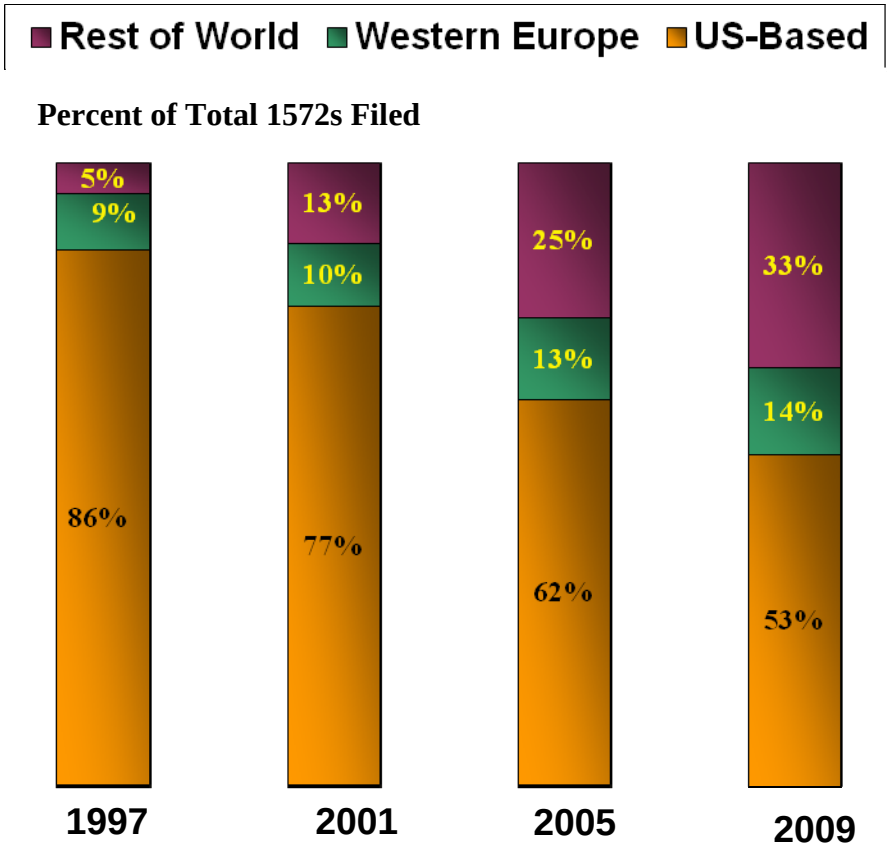
Primary Responses: Globalization, Hedging Risk, Professional Training, Disclosure



During the past decade:

- **The mean number of investigators per active IND has increased 100%**
- **The mean number of patients per active IND has declined 60%**

Sources: Tufts CSDD analysis of FDA's BMIS dbase

Poor Context, Engagement and Connection

Public	**83% believe that clinical research is necessary; Less than 3% say they understand the clinical research process**
Patients (prospective volunteers)	**86% recall seeing/hearing a patient recruitment advertisement recently; Less than 15% report ever learning about clinical trials from their doctor**
Study Volunteers	**88% would participate again; 93% rate site professionalism and quality of care 'excellent'**
Past Study Volunteers	**87% want to know the results of their clinical trial; 79% never again hear from the site after the trial has ended**

Sources: HarrisInteractive; Research!America; CISCRP

Recommendations for NHLBI

- **Include general outreach and education with targeted recruitment programs**
- **Don’t develop and implement initiatives and practices in a vacuum:**
  - **Coordinate and share ideas, experiences and resources with other institutes, agencies, organizations and investigative sites**
  - **Participate in collective public-private efforts to provide general outreach and education**
- **Include in your initiatives the engagement of stakeholders on the periphery of the clinical research enterprise including health care providers, health educators, the media,**

The Challenge

- Physicians are gatekeepers to research participation.
- 87% of physicians are not currently involved in conducting clinical trials.
  - Just 17% report no interest in participating.
- Only 35% of clinicians who agree to recruit for a clinical trial actually refer a patient.

The Literature

- Difficult to summarize; conflicting findings
- Mostly survey data; poor response rates
- Cancer research recruitment predominates
- Few studies examine research coordinator /nurse attitudes
- No randomized trials have been conducted to evaluate methods for improving clinician referrals

Variables SOMETIMES associated with clinician referral behavior

- Patient factors
  - age, younger more likely
  - Disease progression, Stage II most likely
  - Performance status (greater ADL more likely)
  - Patient race/ethnicity, white patients more likely
- Medical practice issues
  - Involve physician practice as research partner
  - Incentives provided
  - Losing a patient from the practice
  - Negative effects on managed care-status

- Fund well designed randomized trials examining interventions to increase clinician recruitment behavior.

NHLBI SHOULD:

- Develop methods to educate all physicians on key aspects of clinical trials, including overall scientific value, benefits, limitations, patient communication, etc.

- Expand racial and ethnic diversity of physicians and RA's conducting research – increase trust in medical

Referral Attitudes

Specific Protocols*

- Overall willingness to refer was high:
  - Low: 68% for RCT with 2 investigational medications
  - High: 93% for RCT with standard medication and placebo control
- Most significant predictors of willingness to refer were:
  - Belief in patients' interest: 6 of 9 studies
  - Perception of study benefit: 5 of 9 studies

General Attitudes**

1. Scientific Merit (importance and future benefit)
2. Patient Benefit (direct or indirect to participant)
3. Contextual Factors (reputation of researchers, institutional support, source of funding).
4. Actual number of referrals predicted by more time spent conducting own research and being a pediatric subspecialist.

*Unpublished

** Dalen, Annett, Brody, & Perryman (2010). Influences upon pediatricians' willingness to refer to clinical research. Open Journal of Clinical Trials

Perceptions of research coordinators on recruitment and [illegible]*

- Race of referring physician impacts recruitment of targeted minority populations.
- White men are most interested in clinical trials, people of color are not interested.
- Staff members feel their interactions are most effective with white males and least effective with Hispanic/Latino patients.

- *HIV research

Guidelines to Improve Inclusion

- Enforcement, tracking, and consequences for non-compliance
- 1986 NIH policy statement encouraging enrollment of women in federally funded research
- 1990 little progress noted by a GAO report
  - NIH created Office of Research on Women's Health and required inclusion of women and minorities unless clear justification for exclusion as well as analyses of results by sex in phase III trials
- 1988 FDA called for studies of whether safety and effectiveness were similar across sex groups
- 2011 FDA guidance "Evaluation of Sex Differences in Medical Device Clinical Studies"
  - Keeping enrollment open until a pre-specified number of women are enrolled
  - Outcomes data analyzed by sex

Future Research Directions

- Increased enrollment in clinical trials
- Sex stratified analyses
- Research to elucidate the paradox of younger women with more adverse outcomes after AMI despite having less severe CAD
- Research to examine sex differences in pathophysiology
- Research focused on subpopulations with greater risk, disproportionate disease burden, and poorer outcomes
- Ongoing monitoring of health care system differences in treatment and outcomes of care

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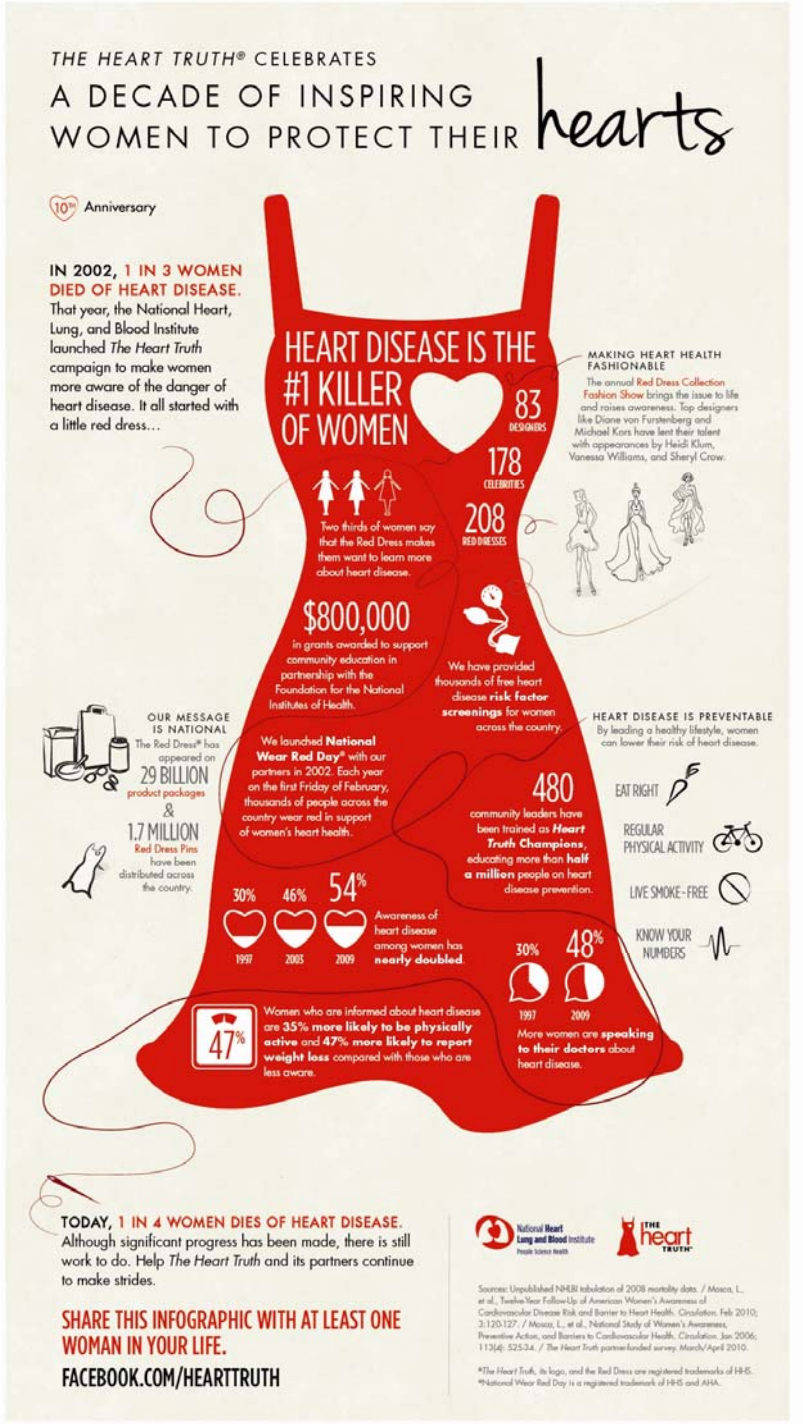
A National Campaign

- To help women understand their risk of heart disease and take action to reduce risk
- Launched 10 years ago
- Partnership of many groups
- The Red Dress
  - Serves as the national symbol for women and heart disease awareness
  - Inspires women to take action to protect their heart health



Specific Device Trials

- Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)
  - 192 women (16% of study population)
- HeartMate II
  - 44 women (23% of study population).
  - Women noted to have a 3-fold increase in stroke risk compared with men and trends toward increased bleeding